reviews

The Role of Anticholinergics in Acute Asthma Treatment*

An Evidence-Based Evaluation

Gustavo J. Rodrigo, MD; and Carlos Rodrigo, MD

The role for anticholinergic medications in acute asthma is not well-defined. Thus, the use of therapy with anticholinergics and β_2-agonists, either simultaneously or in sequence, has produced positive as well as negative results in trials. Therefore, the current recommendations for the use of these drugs in the emergency department (ED) and hospital management of asthma exacerbations are not precise. This review answers the following question: what level of evidence is available in the literature to support the use of anticholinergic medications in combination with β_2-agonists in acute asthma patients? We limited the search on our therapy question to systematic reviews of randomized trials and/or randomized controlled trials not included in the reviews. After an extensive review of the most relevant evidence, the following conclusions may be emphasized. (1) The use of multiple doses of ipratropium bromide are indicated in the ED treatment of children and adults with severe acute asthma. The studies reported a substantial reduction in hospital admissions (30 to 60%; number needed to treat, 5 to 11) and significant differences in lung function favoring the combined treatment. No apparent increase in the occurrence of side effects was observed. (2) The use of single-dose protocols of ipratropium bromide with β_2-agonist treatment produced, particularly in children with more severe acute asthma, a modest improvement in pulmonary function without reduction in hospital admissions; in adults, the data showed a similar increase in pulmonary function with an approximately 35% reduction in the hospital admission rate. In patients with mild-to-moderate acute asthma, there is no apparent benefit from adding a single dose of an anticholinergic medication.

(CHEST 2002; 121:1977–1987)

Key words: acute asthma; anticholinergics; ipratropium bromide; oxitropium bromide

Abbreviations: CI = confidence interval; ED = emergency department; ES = effect size; MDI = metered-dose inhaler; NNT = number needed to treat; PEF = peak expiratory flow; RR = relative risk

The recreational and medicinal properties of atropine have been well-known to many cultures for many centuries.[1] Atropine, in the form of the leaves and roots of *Datura stramonium*, was introduced into Western medicine in the early 1800s by British military officers who had learned of its use for respiratory disorders in India. At that time, stramonium, belladonna, and their alkaloid extract, atropine, had their place in most pharmacopoeias. Only the discovery of the adrenergic agonists in the 1920s displaced these agents as the first-line treatment for asthma and emphysema.

Since the early 1970s, there has been a renewed interest in the use of anticholinergic medications, given the increase in prevalence, morbidity, and mortality of asthma in the past decades, and the need to develop alternatives to therapy with β-agonist agents. The development of less toxic alternatives to atropine led to their wider use in clinical practice. The newer anticholinergic agents are water-soluble, quaternary ammonium compounds that are poorly

*From the Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay (Dr. G. Rodrigo); and Unidad de Cuidado Intensivo (Dr. C. Rodrigo), Asociación Española 1a de Socorros Mutuos, Montevideo, Uruguay.
Manuscript received February 23, 2001; revision accepted September 14, 2001
Correspondence to: Gustavo J. Rodrigo, MD, Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Av 8 de Octubre 3020, Montevideo 11600, Uruguay; e-mail: gurodrig@adinet.com.uy

absorbed, and when they are given by inhalation, they cause fewer systemic side effects.[2–5]

Two factors that have arisen in the past few years have revitalized the interest in anticholinergics bronchodilators. One was a better understanding of the cholinergic mechanisms that control airway caliber in healthy and disease states, and the second one was the development by pharmaceutical chemists of synthetic analogs of atropine that were not appreciably absorbed but retained the anticholinergic properties of the atropine. Thus, physicians worldwide regularly prescribe several anticholinergic agents, including atropine, ipratropium bromide, thiazinamium, oxitropium bromide, and glycopyrrolate. Of these, ipratropium bromide is the most widely studied.

Nevertheless, the role for anticholinergic medications is less well-defined for patients with acute asthma. The use of these drugs as the initial bronchodilator in treatment has been consistently reported[6–9] to be inferior to the use of a β-adrenergic agent on improving airflow in individuals with status asthmaticus. On the contrary, the use of both classes of bronchodilators, either simultaneously or in sequence, has produced positive[10–31] as well as negative trial results.[32–45]

Current recommendations for the use of anticholinergic agents in the emergency department (ED) and hospital management of asthma exacerbations are not precise. For example, the National Asthma Education and Prevention Program expert panel report 2[46 (p66)] stated the following: "Anticholinergics may be considered. Adding high doses of ipratropium bromide (0.5 mg in adults, 0.25 mg in children) to an aerosolized solution of a selective β-agonist has been shown to cause additional bronchodilation, particularly in those with severe airflow obstruction, although some studies did not demonstrate this effect." These conflicting recommendations are based on studies that offer mixed conclusions about whether anticholinergic and β_2-agonist medications lead to a better response than do β_2-agonist medications alone. Although many studies have not shown that combination therapy has a statistically significant beneficial effect, these studies have consistently shown a slightly greater improvement in lung function with combination therapy than with β_2-agonists alone.

To understand the rationale for the use of anticholinergic agents in patients with acute asthma, we must comprehend the mechanisms for bronchoconstriction and dilatation that are mediated by the autonomic nervous system. The majority of autonomic nerves in human airways are branches of the vagus nerve, the efferent preganglionic fibers of which enter the lung at the hilum and travel along the airways into the lung.[47] The efferent innervation is derived from the postganglionic fibers that end in the epithelium, submucosal glands, and smooth muscle of the airways as well as in the vascular structures. Thus, the release of acetylcholine at these sites results in smooth-muscle contraction and the release of secretions from submucosal glands stimulated by their muscarinic receptors.

Cholinergic pathways may be important in regulating acute bronchomotor responses, and many stimuli can provoke bronchoconstriction via vagal pathways. Anticholinergic medications antagonize transmission at the muscarinic receptors. They will only block reflex cholinergic bronchoconstriction and will have no effect on bronchoconstriction resulting from the action of, for example, histamine on airway smooth muscle.

Cholinergic-induced bronchoconstriction appears to involve primarily the large airways, whereas β-agonist medications relax both large and small airway constriction equally. In humans, there are at least three pharmacologically distinct subtypes of muscarinic receptor within the airways, which are known as M_1, M_2, and M_3 receptors.[48,49] The M_1 receptors are present within the parasympathetic ganglion and mediate increased cholinergic transmission. They may facilitate nicotinic transmission or be responsible for maintaining cholinergic tone. Inhibition would reduce cholinergic tone and thus would reduce bronchoconstriction. M_1 receptors also are found on alveolar walls, where their function is unknown. Prejunctional M_2 receptors on the postganglionic nerves act as a negative feedback loop in neuronal transmission. They are activated by the release of acetylcholine and promote its reuptake, thereby limiting the degree of bronchoconstriction produced. These receptors are thought to be dysfunctional in asthma, resulting in exaggerated cholinergic reflexes. The loss of M_2 receptor function has been demonstrated after viral infections. Similar changes can be seen after ozone exposure or antigen challenge.[50] When the M_2 receptors are dysfunctional, the resulting excessive concentrations of acetylcholine at the motor endplate can promote significant bronchoconstriction. Finally, M_3 receptors are located on the airway smooth muscle. The receptor activation leads to a release of calcium ions from intracellular stores and a decrease in intracellular adenosine 3′,5′-cyclic monophosphate levels, resulting in the contraction of airway smooth muscle. M_3 receptors also are located on submucosal glands, where they are likely to be involved in mucus secretion.

Nonselective anticholinergic agents such as atropine, ipratropium bromide, and oxitropium bromide block both the prejunctional (M_2) and postjunctional (M_3) receptors. Thus, due to the blockade of the

prejunctional M_2 receptors, nonselective antagonists may increase the amount of acetylcholine that is released by cholinergic nerve stimulation.[51] This may weaken the effect of the postjunctional M_3 muscarinic receptor blockade on airway smooth muscle and submucosal glands. This suggests that antagonists that bind selectively to M_3 and M_1 receptors may be more effective in inhibiting cholinergic effects in the airways.

The natural anticholinergic, atropine, is rarely used at the present time, however, this drug was used extensively as a nebulized solution by intensivists and ED specialists for years.[52] It is readily absorbed across the oral and respiratory mucosa and, when higher doses are used to maximize bronchodilation, the incidence of dry mouth, blurred vision, urinary retention, nausea, and tachycardia may limit the usefulness of atropine.

The principal anticholinergic agent is ipratropium bromide, a nonselective muscarinic antagonist.[53,54] This drug is topically active, and the compound is poorly lipophilic and not significantly absorbed from the respiratory or GI tract. Ipratropium bromide has no or very little systemic toxicity. It does not appear to affect mucus secretion and ciliary movement. Another significant advantage to ipratropium bromide in the critically ill asthma patient is the lack of increase in heart rate, which does occur with β_2-agonist use.[55] The only remarkable side effect is the inhibition of salivary secretions at high doses. It has no effect on urinary flow or intraocular tension, and possible effects on the eye (*ie*, glaucoma) can be prevented by using a mouthpiece during nebulization. The speed of onset of effect is 3 to 30 min with up to 50% of the response occurring in 3 min and 80% in 30 min, with a peak bronchodilator effect observed within 1 to 2 h, and a duration of action of up to approximately 6 h.[56] In consequence, these properties are appropriate for acute asthma treatment.

Oxitropium bromide is a quaternary anticholinergic compound that is based on scopolamine instead of atropine. It is also a nonselective muscarinic antagonist, with a longer duration of action (up to 8 h) than ipratropium bromide, but it has a slower onset of effect.[57] The peak bronchodilator effect after administration occurs within 1 to 2 h.

Finally, tiotropium bromide is a recently developed, long-acting, selective antimuscarinic medication. This agent is selective for both the M_1 and M_3 receptors. In human bronchi, tiotropium bromide had a similar inhibitory effect with a slow onset of action (peak bronchodilator effect observed after 1.5 to 2 h) and a very prolonged offset compared with ipratropium bromide (the effects persist for 10 to 15 h).[58] Tiotropium bromide has a prolonged inhibitory effect against acetylcholine released from postganglionic nerve endings in the airways, probably via an inhibitory effect on M_3 receptors.

In summary, the potential rationale for the use of a combination of β_2-agonist and anticholinergic agents in patients with acute asthma includes factors such as different sites of action (*ie*, proximal vs distal airways), different mechanisms of action, the onset of bronchodilator effect, and different side-effects profiles. The main purpose of this review is to evaluate the best evidence that is available to determine the role of anticholinergic agents that are added to β_2-agonist agents in the treatment of patients with acute asthma. This article answers the following question: what level of evidence is available in the literature to support the use of anticholinergic medications in combination with β_2-agonist medications in acute asthma patients? We will focus on the analysis of clinical evidence and their implications for clinical practice.

Materials and Methods

The studies found were evaluated based on the following ranking for level of evidence[59]: The best level (level I) included results from large, randomized, controlled trials or systematic reviews of randomized trials. The next level of evidence (level II) would be small, randomized, clinical trials that have insufficient numbers of patients to achieve statistically significant results. Finally, cohort (level III), case control (level IV), and case series (level V) would be considered lower levels of evidence for treatment. In consequence, we limited the initial search on our therapy question to systematic reviews of randomized trials and/or randomized controlled trials not included in the reviews (*ie*, levels I and II). The methodological quality of the trials that were not included in systematic reviews were assessed on the Jadad scale (scale, 0 to 5).[60] A Jadad score of ≥ 3 was considered to be of good quality.

Trials that exclusively studied patients with exacerbations of COPD were excluded. We only reviewed the literature describing the use of anticholinergic agents in children and adults with acute asthma in the ED or a similar acute-care setting. In addition, the languages of publication were restricted to those articles published in English, Spanish, French, Italian, German, or Portuguese.

The outcomes used in acute asthma studies are highly variable and include the results of pulmonary function tests (*ie*, peak expiratory flow [PEF] and FEV_1), admissions to the hospital, return visits after ED discharge, and the administration of medications. Probably, decreasing the need for hospital admission would have the most direct effect on the patients. Outcome measures such as pulmonary function tests, and clinical and physiologic measures, although likely to be correlated with qualitative benefits, may not show us the real therapeutic value of anticholinergic therapy. Therefore, to assess the effectiveness of anticholinergic therapy we selected hospital admission as the primary outcome, and change in pulmonary function test results, clinical or physiologic measures, and adverse effects as secondary outcomes. The pulmonary function effect size (ES) was calculated from data collected as close to 90 to 120 min after the initial treatment as possible. Because the peak bronchodilator effect after the administration of ipratropium bromide and oxitropium

bromide occurs within 1 to 2 h, and because approximately two thirds of patients with acute asthma require 90 min of inhaled β-agonist treatment to have their condition improve sufficiently to be discharged from the ED,[61,62] it is reasonable to expect significant improvement during this time.

The main component of an evidence-based review that distinguishes it from the traditional narrative review is an extensive, structured, and explicit search strategy that is targeted at the identification of all relevant studies.[63,64] Initially, we need to develop a well-defined, clinically relevant, and concise question. In view of previous considerations, we formulated the question as follows: in children and adults, with acute asthma, does the addition of inhaled anticholinergic agents to a standard treatment of β_2-agonist agents decrease the likelihood of hospital admission or improve pulmonary function in the course of the ED visit? Additionally, we analyzed the dose of the anticholinergic treatment and the severity of exacerbation as factors that could influence the treatment response.

The search strategy included the use of MEDLINE (1966 to 2001), EMBASE (1980 to 2001), and CINAHL (1982 to 2001) databases using the following medical subject headings terms: asthma or wheeze and emergency or acute asthma or status asthmaticus and anticholinergic, or ipratropium or atropine, or oxitropium, or glycopyrrolate. Second, we searched in the Cochrane Library for the Database of Systematic Reviews and the Controlled Trials Register. Also, we performed a hand search of the 15 most popular respiratory journals. Finally, we checked the bibliographies of all trials and review articles that had been identified from the databases and medical journals.

Results

Pediatric Studies

The search of the previously described databases produced two systematic reviews about the efficacy of ipratropium bromide and anticholinergic agent use in children with acute asthma.

In the review by Osmond and Klassen,[65] six randomized controlled trials (285 patients) involving pediatric and adolescent patients (age range, 1 to 17 years) with acute asthma were examined to determine the effect of treatment (*ie*, ipratropium bromide plus β-agonists vs β-agonists alone) on clinical and physiologic measures. The review was limited to a single-strategy MEDLINE search of English-language publications between 1966 and 1992, which was supplemented by Science Citation searches. Unpublished data were not considered. Six articles were included (between 1985 and 1988; ED and hospitalized patients). Three of the studies were of high methodological quality (by the scale of Osmond and Klassen[65]). These three studies assessed hospital admissions and pulmonary function. All studies used 250 μg nebulized ipratropium respiratory solution. For the purposes of combining the data, 60 min postintervention was chosen because it was the only assessment time that was common to all three studies. The pooled weighted mean difference showed a 12.5% (95% confidence interval [CI], 6.6 to 18.4%) improvement in FEV_1 percent predicted in the ipratropium bromide group over the control group. The overall ES was 0.88 (95% CI, 0.42 to 1.34). There was no improvement in clinical measurements or the number of hospital admissions. The main limitation of the review was that the combined sample size derived from these three studies and having the highest validity was only 80 patients.

The meta-analysis by Plotnick and Ducharme[66] is a Cochrane Library review that was updated in April 2000. It also was published in a peer-reviewed journal.[67] For this analysis, we selected the Cochrane Library version. The authors assessed the effect of nebulized anticholinergic and β-agonist drugs on hospital admissions or on pulmonary function in children and adolescents with acute asthma in the ED (age range, 18 months to 17 years). With one exception (atropine), the anticholinergic agent used was ipratropium bromide. Only randomized controlled trials were selected for analysis. The literature search included multiple databases (*ie*, MEDLINE, EMBASE, CINAHL, and Cochrane Database of Systematic Reviews). The 13 studies included were performed between 1985 and 1999 in ED settings (1,613 patients). Most were of high quality (*ie*, Jadad quality score, 5). There was no language restriction, and unpublished data were included. The review included the four ED studies identified by Osmond and Klassen.[65] Trials were grouped according to the intensity of the anticholinergic agent protocol. The use of a single dose (250 μg) of a nebulized anticholinergic agent with a β_2-agonist agent did not reduce the number of hospital admissions (relative risk [RR], 0.93; 95% CI, 0.65 to 1.32). However, significant group differences in lung function (*ie*, FEV_1) supporting the combination treatment were observed 60 min (standardized mean difference, 0.57; 95% CI, 0.21 to 0.93) and 120 min (standardized mean difference, 0.53; 95% CI, 0.17 to 0.90) after the single dose of the anticholinergic agent. In contrast, the use of multiple doses of anticholinergic agents with β_2-agonist agents, mainly in children and adolescents who experienced severe exacerbations, reduced the risk of hospital admission by 25% (RR, 0.75; 95% CI, 0.62 to 0.89). Twelve children would need to be given multiple doses of anticholinergic agents in combination with β_2-agonist agents to avoid one hospital admission compared to children given therapy with β_2-agonist agents alone (*ie*, the number needed to treat [NNT]; 95% CI, 8 to 32). When restricting this strategy to children with severe exacerbations, seven children (95% CI, 5 to 20) need to be treated to avoid a hospital admission. At 60 min after the last inhalation of the anticholinergic agent, a weighted mean group difference of 9.7 in the change in FEV_1 percent predicted (95% CI, 5.7 to 13.7) favored the use of anticholinergic agents.

There was no increase in the amount of nausea, vomiting, or tremor in patients who had been treated with anticholinergic agents. The authors concluded the following: (1) a single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations; (2) the use of multiple doses of anticholinergic and β_2-agonist agents improves lung function and would avoid hospital admission in 1 of 12 treated patients; although multiple doses are preferred to single doses, the available evidence only supports their use in children with severe exacerbations of asthma (*ie*, FEV_1, $\leq 55\%$ of predicted); and (3) there is no conclusive evidence for using multiple doses of anticholinergic agents in children with mild-to-moderate asthma exacerbations.

Two randomized, placebo-controlled trials,[31,45] which were published in 2000 and were not included in previous systematic reviews, have investigated the efficacy of therapy with ipratropium bromide in children with acute asthma (Table 1).

Benito Fernández et al[31] studied 102 children (age range, 5 months to 16 years) who had experienced acute attacks of moderate-to-severe asthma in a randomized double-blind trial to compare the efficacy of therapy with ipratropium bromide (two doses of 250 μg each in nebulized form) added to nebulized salbutamol (two doses of 0.2 mg/kg each). The percentage of patients who were admitted to the hospital was higher in the control group than in the ipratropium group (53% vs 35%); however, the difference was not statistically significant (difference, 17%; 95% CI, −2 to 34%). In the subset of patients who had experienced the most severe attacks, the clinical score after treatment and the percentage of admissions were significantly lower in the ipratropium bromide group than in the control group (clinical score, 3.32 vs 2.69, respectively; hospital admissions, 73% vs 39%, respectively; $p < 0.05$). The authors concluded that the beneficial effect of combined treatment was related to a decrease in hospitalization rate, particularly in patients who had experienced severe asthma attacks.

Finally, Sienra Monge et al[45] conducted a randomized trial of 40 children with acute asthma to compare the effects of β_2-agonist agents (*ie*, salbutamol) that had been administered with ipratropium bromide (40 μg administered three times by metered-dose inhaler [MDI]) with those of β_2-agonist agents that had been administered alone. The bronchodilator effects (*ie*, effect on FEV_1) of the administration of salbutamol alone and in combination with ipratropium bromide were considered to be similar in intensity and in action time. However, there was a favorable trend (at 1, 2, 3, and 8 h) to ipratropium bromide treatment (mean difference at 2 h, 0.28; 95% CI, −0.18 to 0.74 L).

In summary, we examined four studies (two systematic reviews and two randomized controlled trials) involving pediatric patients presenting to an ED with acute asthma who had been treated with nebulized anticholinergic agents to determine the effect of treatment on hospital admissions as the primary outcome. The studies also included pulmonary function measurements, the length of time to discharge home from the ED, the number of doses given before hospital discharge, and adverse effects as secondary end points. The addition of multiple doses of anticholinergic agents to treatment with β_2-agonist agents produced an approximately 30% reduction in the number of hospital admissions. In addition, a moderate difference was observed between groups for changes in pulmonary function. The use of multiple doses of anticholinergic medications seems to be indicated in the treatment of

Table 1—*Summary of Main Results of Studies on the Effect of Inhaled Anticholinergic Agents in the Treatment of Pediatric Patients With Acute Asthma**

Study	Patients, No.	Jadad Score	Anticholinergic Protocol	Difference in Hospital Admissions (95% CI)	Change in Pulmonary Function
Benito Fernández et al[31]	102	3	IB (250 μg × 2) NEB	All patients: trend favorable to IB group (35% vs 53% [NS])	NA
				≥ 5 years old: 35% vs 65% favorable to IB group ($p < 0.05$); RR, 0.55 (0.32–0.94); NNT, 4 (2–25)	
				Most severe attacks: 39% vs 73% favorable to IB group ($p < 0.05$); RR, 0.51 (0.29–0.89); NNT, 3 (2–11)	
Sienra Monge et al[45]	30	2	IB (20 μg × 3) MDI	NA	Trend favorable to IB group: FEV_1, 0.28; 95% CI, − 0.18–0.74 L (NS)

*IB = ipratropium bromide; NA = not available; NEB = nebulized; NS = nonsignificant difference.

children and adolescents, and principally those with severe exacerbations of asthma. On the contrary, there was less benefit to adding a single dose of an anticholinergic agent to β-agonist agents in the treatment of children with mild-to-moderate acute asthma.

Adult Studies

Our search found two systematic reviews that assessed the addition of ipratropium bromide to β_2-agonist agents in the treatment of acute adult asthmatic patients in the ED.

Stoodley et al[68] conducted a systematic review to determine whether the addition of inhaled ipratropium bromide to inhaled β-agonist therapy is effective in the treatment of adults (*ie*, persons ≥ 18 years of age) with acute asthma. The review included studies with ED and hospitalized patients. Only randomized controlled trials were selected for analysis. The literature search included multiple databases (*ie*, MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, and Current Contents). The 10 studies included in the review (1,377 patients) were performed between 1985 and 1997 (6 of these were of high quality [Jadad quality score, ≥ 4]). The main outcome measure was pulmonary function collected between 30 and 90 min after the first administered dose of ipratropium bromide. Hospital admission also was considered as an outcome measure. Compared with placebo, the use of ipratropium bromide was associated with a pooled 7.3% improvement in FEV_1 (95% CI, 3.8 to 10.9%), which is equivalent to 30 L/min of PEF. Similarly, the pooled estimate of treatment effect in trials that reported data as PEF was 22.1% (95% CI, 11.0 to 33.2%). When these data were combined using ES as a common measure, the use of ipratropium bromide was associated with an ES of 0.38 (95% CI, 0.27 to 0.48). Studies enrolling patients with more severe airflow obstruction showed greater absolute benefits for combined therapy. For the three trials reporting hospital admission data (1,031 patients), therapy with ipratropium bromide reduced the risk of hospital admission by almost 30% (RR, 0.73 [95% CI, 0.53 to 0.99]; NNT, 23 [95% CI: 12 to 610]). None of the trials reported serious adverse effects that were attributable to treatment. However, a limitation of the review was that the dose-response relationship with ipratropium bromide could not be examined because all studies used 0.5 mg ipratropium bromide administered by nebulizer. Thus, the study design was not consistent with routine ED treatments, which currently include the use of high, frequent, and cumulative doses of bronchodilators.[69,70] In summary, the reviewers found a modest improvement in pulmonary function when ipratropium bromide was added to β_2-agonist treatment, which is associated with a substantial reduction in the hospital admission rate of 30%.

Rodrigo and Rodrigo[71] conducted a systematic review of the literature with a meta-analysis to determine whether therapy with inhaled ipratropium bromide provides additive benefits to adults with acute asthma who are being treated with β-agonist agents in an ED. The main outcome measure was pulmonary function, and hospital admission rate also was evaluated. ES was calculated from the data collected as close as possible to 90 min after the initial dose of ipratropium bromide was administered. Only randomized controlled trials were selected for analysis. The literature search included multiple databases (*ie*, MEDLINE, Current Contents, Science Citation Index, and Cochrane Database of Systematic Reviews). The review included two new ED studies published after 1997. The 10 studies selected (1,483 adults) were performed between 1985 and 1999 (5 studies were of high quality [author's own scale score, ≥ 0.7]). The overall effect was a significant but modest benefit from ipratropium bromide therapy (ES, 0.14; 95% CI, 0.04 to 0.24). This pooled ES was equivalent to a 10% increase (95% CI, 2 to 18%) in pulmonary function in the ipratropium bromide group compared with the placebo group. The analysis showed a substantial improvement with ipratropium bromide therapy in patients with extreme obstruction (*ie*, PEF or FEV_1, < 35%; ES, 0.38; 95% CI, 0.09 to 0.67). In the five trials (1,186 patients) that studied the effect of ipratropium bromide administration on hospital admission, pooled results revealed that therapy with ipratropium bromide reduced admission rates significantly (odds ratio, 0.62 [95% CI, 0.44 to 0.88]; NNT, 18 [95% CI, 11 to 77]). Only six studies reported side effects, and none of them reported serious adverse effects that were attributable to treatment. Again, the therapeutic protocol used in almost all of the studies consisted of a single dose of nebulized ipratropium bromide mixed with β_2-agonist agents, rather than the multiple doses recommended. In summary, this systematic review revealed that the addition of single doses of ipratropium bromide to therapy with β_2-agonists offers a modest improvement in pulmonary function. In addition, the patients with more severe acute asthma benefited substantially from the addition of ipratropium bromide. The fact that the therapeutic protocol used in almost all of the studies consisted of a single dose of nebulized ipratropium bromide (500 μg) may explain why the observed benefit was modest. Despite

this, the early administration of ipratropium bromide with β_2-agonist agents also leads to a 38% reduction in the admission rate.

In addition, we found six randomized controlled trials that had not been included in previous systematic reviews that concerned the effectiveness of anticholinergic agents in adults with acute asthma[27,29,30,36,37,39] (Table 2).

Owens and George[37] enrolled 37 adult patients who had experienced acute asthma attacks. Patients were randomized in a double-blind fashion to receive either one dose of nebulized metaproterenol (5% solution; 0.3 mL) alone or combined with atropine sulfate (2.5 mg) by nebulization. No differences were noted between the two groups regarding changes in FEV_1 and FVC during the observation period (120 min). The authors concluded that therapy with nebulized atropine sulfate yields no additional benefit when added to metaproterenol in the treatment of acute asthma.

Cydulka and Emerman[38] compared a single aerosolized dose of glycopyrrolate (2 mg) plus albuterol with aerosolized albuterol in 125 adult patients who had experienced acute exacerbations of asthma. Both groups received three treatments of aerosolized albuterol, 2.5 mg. Asthmatic patients receiving combination therapy experienced less of a change in FEV_1 than did the control patients (52% vs 82%, respectively; $p < 0.05$).

Diaz et al[40] studied 126 adult patients with acute asthma who had been treated in an ED. All patients received three nebulized treatments with albuterol, 2.5 mg each, over 30 min. Patients were randomized into one of the three following groups: (1) saline solution placebo administered during the three treatments; (2) 2.0 mg atropine sulfate added to the first nebulization and saline solution in the second; and (3) 2.0 mg atropine added to the first and third treatments. At 90 min, there were no significant differences among the three groups on any parameter studied, including improvement of PEF, vital signs, or number of hospital admissions. Combination therapy with atropine sulfate and albuterol offered no significant benefit over the use of albuterol alone in the treatment of patients with acute exacerbations of asthma.

Kamei et al[27] designed a multicenter study to compare the inhalation of fenoterol and fenoterol plus oxitropium bromide delivered by an MDI with a holding chamber to relieve acute attacks of moderate asthma (PEF, < 70% of predicted). They randomized 69 patients to receive fenoterol (1 puff or 200 μg every 1 min for 5 min) or fenoterol plus oxitropium bromide (2 puffs or 200 μg every 1 min for 5 min). At 60 min after inhalation therapy, the pulmonary function of the oxitropium bromide group was significantly improved compared to those of the fenoterol group (mean PEF difference, 51.0 L/min; 95% CI, 1.7 to 100.6). The hospital admission rate was lower in the fenoterol group compared with that in the combination group (6.5% vs 12.1%, respectively), however, the difference was not statistically significant.

Rodrigo and Rodrigo[29] designed a large, double-blind, randomized controlled trial to test the hypothesis that adult patients with acute severe asthma (*ie*,

Table 2—*Summary of Main Results of Studies on the Effect of Inhaled Anticholinergic Agents in the Treatment of Adult Patients With Acute Asthma**

Study	Patients, No.	Jadad Score	Anticholinergic Protocol	Difference in Hospital Admissions (95% CI)	Change in Pulmonary Function (95% CI)
Owens and George[37]	37	3	AT (2.5 mg × 1) NEB	Trend favorable to IB group (12% vs 20% [NS])	NS
Cydulka and Emerman[38]	125	3	GL (2 mg × 1) NEB	NA	Favorable to control group (FEV_1, 52% vs 82% of predicted; $p < 0.05$)
Diaz et al[40]	126	3	AT (2.0 mg × 2) NEB	NS	NS
Kamei et al[27]	69	2	OB (200 μg × 5) MDI + spacer	Trend favorable to IB group (6.5% vs 12.1% [NS])	Favorable to IB group: mean PEF difference, 51.0 L/min (1.7–100.6)
Nakano et al[30]	74	3	OB (200 μg × 5) MDI + spacer	Trend favorable to IB group (13.2% vs 27.8% [NS])	Favorable to IB group: mean PEF difference, 37.8 L/min (15.9–59.8)
Rodrigo and Rodrigo[29]	180	4	IB (24 puffs/h × 3) MDI + spacer	20% vs 36% favorable to IB group ($p = 0.01$); RR, 0.51 (0.31–0.83); NNT, 5 (3–17)	All patients: favorable to IB group: mean PEF difference, 52.3 L/min (27–77.6)

*AT = atropine sulfate; GL = glycopyrrolate; OB = oxitropium bromide. See Table 1 for abbreviations not used in the text.

FEV_1, < 50% of predicted) who are given combination high-dose therapy with ipratropium bromide and β_2-agonist agents will have greater improvement in pulmonary function and fewer hospital admissions than those given β_2-agonist agents alone. One hundred eighty patients who had presented to an ED were assigned in a randomized, double-blind fashion to receive albuterol and placebo or albuterol and ipratropium bromide (both drugs were administered through an MDI and spacer at 10-min intervals for 3 h, 24 puffs, or 2,880 μg albuterol and 504 μg ipratropium bromide each hour). At the end of treatment, subjects who had received ipratropium bromide had an overall 48.1% greater improvement in FEV_1 (95% CI, 19.8 to 76.4%) than those in the control group. At 90 min, the response in the ipratropium bromide group was significantly higher compared to that in the control group (mean PEF difference, 52.3 L/min; 95% CI, 27.0 to 77.6). At the end of the protocol (*ie*, after 3 h), 39% of patients in the control group and 20% of patients in the ipratropium bromide group were admitted to the hospital. The use of high doses of ipratropium bromide reduced the risk of hospital admission by 49% (RR, 0.51 [95% CI, 0.31 to 0.83]; NNT, 5 [95% CI, 3 to 17]). Kaplan-Meier estimated curves of the proportion of patients who reached the hospital discharge threshold during the 3 h of treatment showed a significant difference in favor of the ipratropium bromide group. A subgroup analysis showed that patients who were the most likely to benefit from the addition of high doses of ipratropium bromide were those with more severe obstruction (*ie*, FEV_1, ≤ 30% of predicted; RR, 0.61; 95% CI, 0.38 to 0.99) and longer duration of symptoms before the ED presentation (*ie*, ≥ 24 h; RR, 0.32; 95% CI, 0.126 to 0.64). The authors concluded that there was a significant advantage when high doses of ipratropium bromide and albuterol are combined in the ED treatment of adults with acute severe asthma.

Nakano et al[30] compared the outcomes of adults with acute severe asthma (*ie*, PEF, < 50% of predicted) who had been treated with 4 puffs (400 μg) albuterol every 20 min for three doses plus 4 puffs of oxitropium bromide (400 μg) with each of the three salbutamol doses to the administration of salbutamol alone by means of an MDI with a spacer device. A randomized, single-blind, placebo-controlled trial was performed in 74 adult patients presenting to the ED for treatment. The increase in PEF over the course of treatment was significantly greater in the oxitropium bromide-plus-salbutamol group. The mean absolute difference in PEF at 120 min for patients receiving combination therapy compared with those receiving salbutamol alone was 37.8 L/min (95% CI, 15.9 to 59.8). They found that patients with more severe asthma (*ie*, baseline PEF, < 200 L/min) benefited from the addition of oxitropium bromide to salbutamol (mean difference, 44 L/min; 95% CI, 11 to 75). In addition, the proportion of need for additional treatment was less in the combination group than in the salbutamol group (odds ratio, 0.32; 95% CI, 0.11 to 0.90). Finally, there was a trend toward a reduction of hospitalization among patients receiving combination therapy compared to single-agent therapy (13.2% vs 27.8%, respectively), but this difference did not reach statistical significance.

In summary, we examined two systematic reviews and six randomized controlled trials involving adult patients with acute asthma who were treated with inhaled anticholinergic agents (*ie*, atropine, ipratropium, oxitropium, or glycopyrrolate). The studies included pulmonary function, hospital admission rate, and the need for additional treatment as end points (Table 2). We concluded that there was a dose-response relationship. Thus, the use of single-dose protocols showed a modest improvement in pulmonary function with an approximately 35% decrease in hospital admissions (NNT, approximately 20) compared to patients receiving albuterol alone. On the contrary, the addition of multiple doses of anticholinergic agents (*ie*, ipratropium and oxitropium) to β_2-agonist treatment showed a larger difference among groups in pulmonary function, with a approximately 50% reduction in hospital admissions (NNT < 8) for the combined therapy. Patients with more severe asthma showed a substantial improvement following treatment with anticholinergic agents. On the contrary, the studies that used atropine and glycopyrrolate did not show a significant advantage for the β-agonist treatment.

Implications for Clinical Practice

Overall, the analysis of the literature suggests that inhaled anticholinergic agents provide an additional benefit to children and adults with acute asthma who are treated with β_2-agonist medications in an ED. After an extensive review of the most relevant evidence, the following conclusions may be emphasized:

1. The use of multiple-dose protocols of ipratropium bromide seems indicated in the initial ED treatment of children and adults with severe acute asthma (*ie*, FEV_1, < 50%). The studies reported an important reduction in hospital admission rates (30 to 60%; NNT, 5 to 11) using therapy with albuterol plus ipratropium bromide. Regarding lung function, significant differences exceeding half an SD in change (PEF variation, 50 L/min) favoring the combination treatment also were observed after 60 to

90 min of treatment. The amount of this improvement is probably clinically significant.[72,73] An examination of the protocols of the trials reveals that repeated doses of nebulized ipratropium bromide were usually given as follows: 250 μg per dose every 20 min in the treatment of children; and 500 μg per dose every 20 min in nebulized form or 4 puffs (80 μg) every 10 to 20 min via an MDI and spacer in the treatment of adults. Also, 4 puffs of oxitropium bromide (400 μg) every 20 min administered by an MDI and spacer was equally effective. No apparent increase in the occurrence of side effects was observed. Consequently, the benefits prevail over the harm associated with its use.

2. The use of single-dose protocols of anticholinergic agents with β_2-agonist treatment produced, particularly in children with more severe acute asthma, a modest improvement in pulmonary function without a reduction in the hospital admission rates. In adults, the data showed a similar increase in pulmonary function with an approximately 35% reduction in the hospital admission rate (NNT, approximately 20). On the contrary, in patients with mild-to-moderate acute asthma, there is no apparent benefit from adding a single dose of anticholinergic agents.
3. In adult patients with acute asthma, there is no benefit from adding one or two doses (4 mg) of nebulized atropine sulfate or a single dose of nebulized glycopyrrolate
4. With regard to the response predictors to combined therapy, Garrett et al[21] showed that factors predicting a poor bronchodilator response were the frequent use of inhaled β_2-agonist agents before presenting at the ED, increased severity and duration of the attack, and older age. However, other studies did not show these findings. Thus, in the Nakano et al[30] study, the benefit of combined therapy was equally evident in the prior use of β_2-agonist agents. As they stated, "the independent benefit of the anticholinergics is consistent with the proposal that muscarinic receptors are described in the large airways, and β_2-receptores are mainly in the small airways." In the same way, Rodrigo and Rodrigo[29] found that the use of inhaled β_2-agonist agents before presenting at the ED did not modify the pulmonary function response and the admission rate. Thus, patients treated with ipratropium bromide had FEV_1 increases regardless of their previous use of β_2-agonist medications.
5. Ipratropium bromide is not a particularly expensive drug, and the addition of a multiple-dose protocol to inhaled β_2-agonist therapy for acute severe asthma patients would result in savings in health-service resources. Therefore, a cost-effectiveness analysis by Lord et al[74] on inhaled anticholinergic agents for the treatment of acute childhood and adolescent asthma estimated a net saving of ≤ £80 per severe case that was treated (95% CI, £3 to £157). Further analysis is needed to determine whether combination therapy in adults with acute asthma reduces costs. In addition to efficacy, the methods of drug administration will influence the decision to use anticholinergic agents for acute asthma. The costs for nebulized therapy are necessarily higher than for MDI therapy because the administration of the nebulization therapy must be performed by trained healthcare personnel, and the tubing and masks used for nebulization must be discarded after patient use. It has been shown that the routine substitution of an MDI with a spacer device saves hospital resources.[75] There is significant evidence that anticholinergic and β_2-agonist medications can be delivered effectively to patients with acute asthma by means of an MDI with a spacer in less time, with lower costs, and with minimal toxicity.

References

1 Gandevia B. Historical review of the use of parasympatholytic agents in the treatment of respiratory disorders. Postgrad Med J 1975; 51(suppl):13–20
2 Gross N, Skorodin M. Anticholinergic, antimuscarinic bronchodilators. Am Rev Respir Dis 1984; 129:856–870
3 Ziment I, Au JP. Anticholinergic agents. Clin Chest Med 1986; 7:454–458
4 Weber R. Role of anticholinergics in asthma. Ann Allergy 1990; 65:348–350
5 Beakes DE. The use of anticholinergics in asthma. J Asthma 1997; 34:357–368
6 Leahy BC, Gomm SA, Allen SC. Comparison of nebulized salbutamol with nebulized ipratropium bromide in acute asthma. Br J Dis Chest 1983; 77:159–163
7 Karpel JP, Appel D, Breidbart D, et al. A comparison of atropine sulfate and metaproterenol sulfate in the emergency treatment of asthma. Am Rev Respir Dis 1986; 133:727–729
8 Murray PT, Corbridge T. Pharmacotherapy of acute asthma. In: Hall JB, Corbridge TC, Rodrigo C, et al, eds. Acute asthma: assessment and management. New York, NY: McGraw-Hill, 2000; 139–160
9 Rodrigo C, Rodrigo GJ. Inhaled therapy in nonintubated patients. In: Hall JB, Corbridge TC, Rodrigo C, et al, eds. Acute asthma: assessment and management. New York, NY: McGraw-Hill, 2000; 161–178
10 Ward MJ, Fentem PH, Roderick-Smith WH, et al. Ipratropium bromide in acute asthma. BMJ 1981; 282:598–600
11 Beck R, Robertson C, Galdes-Sebaldt M, et al. Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. J Pediatr 1985; 107:605–608

12 Bryant DH. Nebulized ipratropium bromide in the treatment of acute asthma. Chest 1985; 88:24–29
13 Ward MJ, McFarlane JT, Davies D. A place for ipratropium bromide in the treatment of severe acute asthma. Br J Dis Chest 1985; 79:374–378
14 Rebuck AS, Chapman KR, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airway disease in the emergency room. Am J Med 1987; 82:59–64
15 Roeseler J, Reynaert MS. A comparison of fenoterol and fenoterol-ipratropium nebulization treatment in acute asthma. Acta Ther 1987; 13:571–578
16 Reisman J, Galdes-Sebalt M, Kazim F, et al. Frequent administration by inhalation of salbutamol and ipratropium bromide in the initial management of severe acute asthma in children. J Allergy Clin Immunol 1988; 81:16–20
17 O'Driscoll BR, Taylor RJ, Horsley MG, et al. Nebulized salbutamol with and without ipratropium bromide in the acute airflow obstruction. Lancet 1989; 1:1418–1420
18 Louw SJ, Goldin JG, Isaacs S. Relative efficacy of nebulised ipratropium bromide and fenoterol in acute severe asthma. S Afr Med J 1990; 77:24–26
19 Teale C, Morrison JF, Muers MF, et al. Response to nebulized ipratropium bromide and terbutaline in acute severe asthma. Respir Med 1992; 86:215–218
20 Schuh S, Johnson DW, Callahan S, et al. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. J Pediatr 1995; 126:639–645
21 Garrett JE, Town GI, Rodwell P, et al. Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma. J Allergy Clin Immunol 1997; 100:165–170
22 Quereshi FA, Zaritsky A, Lakkis H. Efficacy of nebulized ipratropium in severe asthmatic children. Ann Emerg Med 1997; 29:205–211
23 Calvo GM, Calvo AM, Marin HF, et al. It is useful to add an anticholinergic treatment to beta 2-adrenergic medication in acute asthma attack? J Investig Allergol Clin Immunol 1998; 8:30–34
24 Lin RY, Pesola GR, Bakalchuk L, et al. Superiority of ipratropium plus albuterol over albuterol alone in the emergency department management of adult asthma: a randomized clinical trial. Ann Emerg Med 1998; 31:208–213
25 Quereshi F, Pestian J, Davis P, et al. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. N Engl J Med 1998; 339:1030–1035
26 Lanes SF, Garret JE, Wentworth CE, et al. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998; 114:365–372
27 Kamei T, Fujita J, Okada H, et al. Comparison between fenoterol and fenoterol plus oxitropium bromide delivered by metered-dose inhaler with Inspirease to relieve acute asthma attack. J Asthma 1999; 36:67–75
28 Zorc JJ, Pusic MV, Ogborn CJ, et al. Ipratropium bromide added to asthma treatment in the pediatric emergency department. Pediatrics 1999; 103:748–752
29 Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. Am J Respir Crit Care Med 2000; 161:1862–1868
30 Nakano Y, Enomoto N, Kawamoto A, et al. Efficacy of adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered-dose inhaler with spacer device in adults with acute severe asthma. J Allergy Clin Immunol 2000; 106:472–478
31 Benito Fernández J, Mintegui Raso S, Sánchez Echaniz J, et al. Eficacia de la administración precoz de bromuro de ipratropio nebulizado en niños con crisis asmática. Ann Esp Pediatr 2000; 53:217–222
32 Guill MF, Maloney MJ, DuRant RH. Comparison of inhaled metaproterenol, inhaled atropine sulfate, and their combination in treatment of children with acute asthma. Ann Allergy 1987; 59:367–371
33 Higgins RM, Stradling JR, Lane DJ. Should ipratropium bromide be added to β-agonists in the treatment of acute severe asthma? Chest 1988; 94:718–722
34 Watson WTA, Becker AB, Simons FER. Comparison of ipratropium solution, fenoterol solution, and their combination administered by nebulizer and face mask to children with acute asthma. J Allergy Clin Immunol 1988; 82:1012–1018
35 Phanichyakam P, Kraisarin C, Sasisakulporn C. Comparison of inhaled terbutaline and inhaled terbutaline plus ipratropium bromide in acute asthmatic children. Asian Pac J Allergy Immunol 1990; 8:45–48
36 Summers QA, Tarala RA. Nebulized ipratropium in the treatment of acute asthma. Chest 1990; 97:430–434
37 Owens M, George R. Nebulized atropine sulfate in the treatment of acute asthma. Chest 1991; 99:1084–1087
38 Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of asthma. Ann Emerg Med 1994; 23:270–274
39 Karpel JP, Schacter EN, Fanta CH, et al. A comparison of ipratropium and albuterol vs albuterol alone for the treatment of acute asthma. Chest 1996; 110:611–616
40 Diaz JE, Dubin R, Gaeta TJ, et al. Efficacy of atropine sulfate in combination with albuterol in the treatment for acute asthma. Acad Emerg Med 1997; 4:107–113
41 FitzGerald JM, Grunfeld A, Pare PD, et al. The clinical efficacy of combination nebulized anticholinergic and adrenergic bronchodilators vs. nebulized adrenergic bronchodilator alone in acute asthma. Chest 1997; 111:311–315
42 McFadden ER, El Sanadi N, Strauss L, et al. The influence of parasympatholytics on the resolution of acute attacks of asthma. Am J Med 1987; 102:7–13
43 Ducharme FM, Davis GM. Randomized controlled trial of ipratropium bromide and frequent low doses of salbutamol in the management of mild and moderate acute pediatric asthma. J Pediatr 1998; 133:479–485
44 Weber EJ, Andrew Levitt M, Covington JK, et al. Effect of continuously nebulized ipratropium bromide plus albuterol on emergency department length of stay and hospital admission rates in patients with acute bronchospasm: a randomized controlled trial. Chest 1999; 115:937–944
45 Sienra Monge JJ, Bermejo Guevara MA, del Rio Navarro BE, et al. Grado y duración de la broncodilatación mediante la administración de un agonista beta 2 solo vs. un agonista beta 2 más bromuro de ipratropio en niños con asma aguda. Rev Alerg Mex 2000; 47:26–29
46 National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health, April 1997; Publication No. 55–4051
47 Richardson JB. Nerve supply to the lungs. Am Rev Respir Dis 1979; 119:785–802
48 Barnes PJ, Minette P, Maclagan J. Muscarinic receptor subtypes in the airways. Trends Pharmacol Sci 1988; 9:412–416
49 Barnes PJ. Muscarinic receptor subtypes in airways. Life Sci 1993; 52:521–527
50 Fryer AD, Jacoby DB. Effect of inflammatory cell mediators on M_2 muscarinic receptors in the lungs. Life Sci 1993; 52:529–536
51 Patel HJ, Barnes PJ, Takahashi T, et al. Evidence for

prejunctional muscarinic autoreceptors in human and guinea pig trachea. Am J Respir Crit Care Med 1995; 152:872–878
52 Siefkin AD. Optimal pharmacologic treatment of the critically ill patients with obstructive airways disease. Am J Med 1996; 100(suppl):545–615
53 Schlueter DP. Ipratropium bromide in asthma: a review of the literature. Am J Med 1986; 81(suppl):55–59
54 Chapman KR, Smith DL, Rebuck AS, et al. Hemodynamic effects of inhaled ipratropium bromide alone and combined with an inhaled β-agonist. Am Rev Respir Dis 1985; 132:845–847
55 Cugell DW. Clinical pharmacology and toxicology of ipratropium bromide. Am J Med 1986; 81:18–22
56 Gross NJ. Ipratropium bromide. N Engl J Med 1988; 319: 486–494
57 Peel ET, Cheong AB, Broderick N. A comparison of oxitropium bromide and ipratropium bromide in asthma. Eur Respir Dis 1984; 65:106–108
58 Barnes PJ. Tiotropium bromide: a new long-acting anticholinergic bronchodilator. In: Barnes PJ, Buist AS, eds. The role of anticholinergics in chronic obstructive pulmonary disease and chronic asthma. Maidenhead, UK: Gardiner-Caldwell Communications, 1997; 126–136
59 Guyatt GH, Sackett DL, Sinclair JC, et al. User's guides to the medical literature IX: a method of grading health care recommendations. JAMA 1995; 274:1800–1804
60 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized controlled: is blinding necessary? Control Clin Trials 1995; 134:1–12
61 Strauss L, Hejal R, Galan G, et al. Observations on the effects of aerosolized albuterol in acute asthma. Am J Respir Crit Care Med 1997; 155:454–458
62 Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. Chest 1998; 113:593–598
63 Sackett DL, Scott Richardson W, Rosenberg W, et al. Evidence-based medicine: how to practice and teach EBM. New York, NY: Churchill Livingstone, 1998
64 Rowe BH, Travers AH, Holroyd BR, et al. Nebulized ipratropium bromide in acute pediatric asthma: does it reduce hospital admissions among children presenting to the emergency department? Ann Emerg Med 1999; 34:75–85
65 Osmond MH, Klassen TP. Efficacy of ipratropium bromide in acute childhood asthma: a meta-analysis. Acad Emerg Med 1995; 2:651–656
66 Plotnick LH, Ducharme FM. Combined inhaled anticholinergics agents and beta-2-agonists for initial treatment of acute asthma in children (Cochrane Review). In: The Cochrane Library, issue 1, 2001. Oxford, UK: Update Software, 2001
67 Plotnick LH, Ducharme FM. Should inhaled anticholinergics be added to β_2-agonists for treating childhood and adolescent asthma? A systematic review BMJ 1998; 317:971–977
68 Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a meta-analysis of randomized clinical trials. Ann Emerg Med 1999; 34:8–18
69 Rodrigo G, Rodrigo C. Ipratropium bromide in acute asthma: small beneficial effects [letter]? Chest 1999; 115:1482
70 Silverman R. Ipratropium bromide in emergency management of acute asthma exacerbation [letter]. Ann Emerg Med 2000; 35:197–198
71 Rodrigo G, Rodrigo C. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999; 107:363–370
72 Santanello NC, Zhang J, Seidenberg B, et al. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999; 14:23–27
73 Karras DJ, Sammon ME, Terregino CA, et al. Clinically meaningful changes in quantitative measures of asthma severity. Acad Emerg Med 2000; 7:327–334
74 Lord J, Ducharme FM, Stamp RJ, et al. Cost effectiveness analysis of inhaled anticholinergics for acute childhood and adolescent asthma. BMJ 1999; 319:1470–1471
75 Bowton DL, Goldsmith WM, Haponick EF. Substitution of metered dose inhalers for hand held nebulizers: success and cost savings in a large acute care hospital. Chest 1992; 101:305–308